UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JUN 19 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No. 097601-9, Propargite - Dermal Sensitization in Guinea Pigs (With Rovral) -LD_{50} Study in Monkeys, Preliminary Reports on the Metabolism (in vivo and in vitro) of ^{14}C Propargite in Rats, Rabbits, and Monkeys

TOX Chem No.: 130I
TOX Project No.: 9-0894
Record Nos.: 240228, 240229

FROM: John Doherty 5/9/89
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: Sepeher Haddad, PM 71
Registration Division (H7508C) 6/30/89

THROUGH: Edwin Budd
Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

The Uniroyal Chemical Company has submitted several studies in support of their product Omite (propargite). Refer to list attached. These studies were reviewed and Data Evaluation Reports prepared. The following comments apply.

Toxicology Branch Comments

1. The in vivo metabolism study in rats, rabbits, and monkeys was a preliminary report and not reviewed in detail. The registrant should be advised to consult the current guidelines for submitting toxicity studies and prepare a report based on these recommendations.

   This study is considered deficient based on the information, however, provided because only one or two females were used per test condition. Guidelines studies recommend 5 of each sex.

   The data, however, may be upgraded to an acceptable level pending receipt and review of the final report and when taken together with the evaluation of other metabolism data with propargite.

2. The in vitro metabolism study was determined to be SUPPLEMENTARY. The useful information generated related the similar patterns of metabolism in each of the three species tested (rat, rabbit, and monkey). In vitro studies are, however, limited in usefulness in meeting regulatory requirements because of the complexity of the in vivo situation where interacting factors such as absorption, distribution and elimination of the compound all contribute to the overall metabolism and excretion.

3. The guinea pig sensitization (Beuhler) study did not indicate that Omite 30W was a sensitizer or interacted with the product Rovral to cause sensitization.

4. Propargite was demonstrated to have an LD_{50} in monkeys in excess of 5000 mg/kg. The study was submitted as a draft report and as such is UNACCEPTABLE. The final report of this study may potentially be upgraded to SUPPLEMENTARY if submitted. The study utilized only one monkey (female) at each dose level.

Attachments

Studies Submitted

Dermal Sensitization - Guinea Pigs (with Rovral) Arthur D. Little, ADL Ref. 62323 January 11, 1989	No evidence that Omite 30W caused contact sensitization in a Buehler type assay or cross-reacted with Rovral. Rovral was regarded as a weak contact allergen. MINIMUM
Acute Oral Toxicity - Monkeys Battelle #8881 December 23, 1988	No deaths at 5000 mg/kg. Doses tested 18, 105, 500, 1000, and 5000 mg/kg (single female at each dose). Only symptom: loose stools. Test material was 60% propargite and 40% unidentified. UNACCEPTABLE (Study is a draft report, final may be potentially upgraded to SUPPLEMENTARY).
Metabolism - In Vitro in Rat, Rabbit and Monkey Liver Homogenate and S-9 Fraction Battelle #N4867-2000 December 1988	Omite glycol ether, bis glycol ether sulfate and polar metabolites resulting from liver homogenate and S-9 preparation. No real difference in in vitro metabolism in rat, rabbit, or monkey liver. SUPPLEMENTARY
Metabolism - In Vivo in Rat, Rabbit, and Monkey Battelle #8881 December 29, 1988	Preliminary report of study presented. Full review pending receipt and review of final report.

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Reviewed By: John Doherty 5/9/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Edwin Budd 5/26/89
Section I, Toxicology Branch I - IRS (H7509C) Acting

DATA EVALUATION REPORT

Study Type: 81-6: Sensitization - Guinea Pigs

TOX Chem No.: 130I
470A
MRID No.: 409753-10

Test Material: Omite 30W (Lot #804G281) provided by Rhone-Poulenc and Rovral provided by Uniroyal (lot [redacted] # not provided).

Synonyms: Omite (propargite)

Study Number: ADL Ref. 62323

Sponsor: Uniroyal Chemical Company

Testing Facility: Arthur D. Little

Title of Report: Evaluation of Omite and Rovral for Repeated Dose Dermal Irritation and Contact (Cross)-Sensitization of Guinea Pigs.

Authors: C.L. Berman; J.A. DiNunzio; R. Latta and M. Mazrimas

Report Issued: January 11, 1989

Conclusions:

No evidence that Omite 30W is a contact allergen or cross-reacts with Rovral. Rovral was considered to be a weak contact allergen.

Classification: CORE-MINIMUM

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

A statement signed by Denise Hayes, Quality Assurance Officer attested that six inspections were made and that the findings of these inspections were reported to management on three occasions.

Review

The purpose of this study was to follow up on reports that workers in nectarine fields in California may have developed skin rashes as a result of exposures to Omite and/or Rovral. The study design was based on Beuhler's method for assessing sensitization in guinea pigs.

A dose range-finding study was first run to select the highest nonirritating dose levels of both Omite and Rovral. In this dose range-finding study, two groups of four guinea pigs were prepared by having their backs shaved and doses of 0.05, 0.1, 1.0 and 5.0 percent in distilled water of Rovral or Omite were applied to selected areas to each of the four pigs in the group. It was determined that a dose of 5.0 percent of Rovral and 0.1 percent of Omite were the highest nonirritating dose levels.

The main study consisted of three groups of 10 guinea pigs (female albino guinea pigs, outbred Dunkin-Hartley strain, purchased from Hazleton Research Products, Inc., Denver, PA). Their age was not specified but they were reported to weigh 250 to 300 g at arrival. The three groups consisted of a group serving as the control dosed with distilled water, a group dosed with 0.1 percent Omite 30W in distilled water, and a group dosed with Rovral in distilled water. The treatment consisted of preparing the flank region of each guinea pig by shaving and cleansing with ethanol. The induction phase consisted of applying the test material in a 2 x 2 g patch of Webril cotton and placing on the left flank. The patch was occluded with Blenderm tape and secured with an Elastoplast elastic bandage. The test material was kept in contact for 6 hours before removal and cleansing with water. A total of nine induction applications were made 3 times a week for 3 weeks. The guinea pigs were examined for dermal irritation reactions on removal of each patch.

The challenge application was made 2 weeks following the ninth induction application. The right flank was shaved and cleansed with ethanol. Each guinea pig was challenged with both Omite 30W and Rovral by applying 2 x 2 cm cotton patches saturated with each formulation. The challenge application was made to the right flanks of each guinea pig. The challenge patches were kept in place for 6 hours. Approximately 24 hours after removal of each patch, the area was treated with a depilatory and the area was evaluated for dermal reactions 2 hours later. Additional evaluations of the challenge patch area were made 48 and 72 hours after the application of the challenge patch.

Results:

1. Reactions During the Induction Phrase--No reactions to the vehicle (distilled water) were evident during the induction phase. The reactions to both Omite and Rovral were reported as being "scattered mild redness at the patch site." The severity index for both Omite and Rovral treated guinea pigs increased with time such that both reached a maximum of 1 (mild) on a scale of 3 (intense).

2. Reactions Following the Challenge Application--Following treatment with the challenge dose of Omite (0.1% solution) both the control group 1 and the Omite dose group 2 showed signs of slight redness at 24 hours. The group dosed with Rovral had mild redness at 24 hours and slight redness at 48 hours.

   Following treatment with a challenge dose of Rovral, the control and Omite treated groups developed slight redness (0.05 and 0.1 severity scores, respectively) at 24 hours but had no irritation score afterwards. The group 3 dosed with Rovral had scores of 0.25, 0.25, and 0.1 at 24, 48, and 72 hours, respectively.

Conclusion:

This study is CORE MINIMUM. The study demonstrates that Omite 30W did not cause contact sensitization or cross-react with Rovral under the conditions of this study. Rovral alone was considered to be a "weak contact allergen" based on the presence of a "minimal" reaction to the challenge dose that persisted to 72 hours.

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Reviewed By: John Doherty John Doherty 5/30/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Edwin Budd
Section I, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: 81-1: Acute Oral Toxicity - Monkeys

TOX Chem No.: 130I
MRID No.: 408825-06

Test Material: Omite, Technical Grade Lot No. BA-2-58 (See review for comments on purity)

Synonyms: Propargite

Study Number: Project No. 8881

Sponsor: Uniroyal Chemical Company

Testing Facility: Battelle, Columbus, Ohio

Title of Report: "Omite Range-Finding Study in the Monkey" (Battelle Letter Report).

Author: Jerry D. Johnson

Report Issued: December 23, 1988

Conclusions:

No deaths at 5000 mg/kg. Only symptoms were loose stools. Necropsy was not remarkable. LD_{50} > 5000 mg/kg. Doses tested 18, 105, 500, 1000, and 5000 mg/kg (single female monkey at each dose level). N.B.: The test material was 60% propargite, 40% unidentified.

Classification: UNACCEPTABLE (Study is a draft report. FInal report may potentially be ungraded to SUPPLEMENTARY.)

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement: None provided.

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Review

Five female Cynomolgus monkeys were dosed with either 18, 105, 500, 1000, or 5000 mg/kg, one monkey per dose level, of Omite technical dissolved in corn oil and administered orally at a dosage level of 5 ml/kg. They were observed for 7 days.

None of the monkeys died. The only symptoms reported related to the passing of soft stools. It was not established if this was due to the combination of Omite and corn oil. The monkey dosed with 5000 mg/kg lost weight initially, but recovered. No definite effects were evident as indicated by hematology and clinical chemistry assessment.

Analysis of the test material indicated that two major peaks resulted in the HPLC chromatogram in the area of where pure Omite standard elutes. This indicated that the Omite tested was approximately 60 percent pure.

Conclusion:

This submission is a draft report and as such is UNACCEPTABLE in this form. The sample used was of 60 percent (approximately) purity and the impurity was not identified. As some useful information was provided in that Omite was demonstrated to be of a low order of toxicity to the monkey, the study if submitted in a final form may potentially be upgraded to SUPPLEMENTARY. Since acute toxicity in the monkey is not required for regulatory purposes there is no need to repeat this study.

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Reviewed By: John Doherty John Doherty 5/9/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Edwin Budd 5/10/89
Section I, Toxicology Branch I - IRS (H7509C) Acting

DATA EVALUATION REPORT

Study Type: Series 85: Metabolism

TOX Chem No.: 130I
MRID No.: 409825-06

Test Material: ^{14}C Propargite (Phenyl-U-^{14}C)

Synonyms: Omite

Study Number: N4867-2000

Sponsor: Uniroyal Chemical Company

Testing Facility: Battelle, Columbus, Ohio and Uniroyal

Title of Report: In Vitro ^{14}C-Omite Comparative Metabolism Study in Liver Homogenate and S-9 Fraction from Rats, Rabbits, and Monkeys.

Authors: J.D. Johnson, M.J.W. Chang and J.A. Killinger

Report Issued: December 21, 1988

Conclusions:

The study demonstrated that the rat, rabbit, and monkey liver homogenate and S-9 preparations all have the same profile for ^{14}C products derived from ^{14}C Propargite. The products were Omite-glycol ether, and bis-glycol ether sulfate as well as two polar compounds. No difference in the metabolism of Propargite by rat, rabbit, or monkey liver was evident.

Classification: SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

A statement signed by Ramona A. Mayer, Manager Quality Assurance Unit at the Battelle Laboratory attested that some 11 phases of the study were inspected.

Review

This project was conducted in two phases and in two different laboratories. The in vitro aspect of the study was conducted at the Battelle facilities and once the metabolism incubation periods were completed the samples were frozen and sent to the Uniroyal Laboratories for completion of analysis.

Part I. Preparation of Liver Homogenates and S-9 Fraction from Rat, Rabbit and Monkey and Incubation Conditions for ^{14}C Omite Metabolism at the Battelle Facilities

The liver was removed from a single female rat (Sprague-Dawley, CD/BR approximately 250 g in weight), rabbit (New Zealand White 2.8 kg) and monkey (Cynomolgus, 1.9 to 2.8 kg) and homogenized in ice cold 0.25 M sucrose 0.05 M Tris buffer (pH 7.5). The homogenate was filtered through three layers of gauze. The filtrate was used as collected for the experiments where the crude homogenate was used. The S-9 preparation was prepared by centrifuging the filtrate 9000 x g for 20 minutes and the supernatant collected for the experiments using the S-9 preparation.

The basic protocol for this study consisted of incubating both the S-9 fraction and homogenate from each of the three species at two concentrations of ^{14}C Propargite (8.0 and 30 nmoles/mL) for three (S-9 preparation) time intervals (15, 30, and 60 minutes for a total of 18 incubations) or for four (homogenate preparation) time intervals (15, 30, 60, and 120 minutes for a total of 24 incubations). Apparently only one sample for each incubation time was prepared.

Details were provided regarding the substrate preparation and solution analysis. This indicated that the radioactive material was 86.3 percent radiochemical purity with there being several smaller peaks (as assessed by HPLC coupled to a liquid scintillation counter). The total ^{14}C accounted for was 95.6 percent. Data were presented to indicate that the actual concentrations of Omite in the metabolic test preparations were within $\pm$ 2 percent of the targeted concentrations.

Part II. Analysis of the Homogenate for ^{14}C Metabolites (Conducted at the Uniroyal Facilities)

The samples from the S-9 and homogenate as received from the Battelle facility were filtered through a 0.2 micron nylon 66 filter and the filtrate was directly injected into HPLC for profiling and analysis of ^{14}C distribution.

The report from the Uniroyal laboratory (refer to Overall Summary prepared by Arthur M. Doweyko and N.J. Tortora, January 1989) states that "three major components were observed in all the chromatographic analyses: OMITE, OMITE-glycol either, and the bis-glycol ether sulfite." The ether and ether sulfite as well as two polar components (which were reported as being present to varying degrees) were regarded as breakdown products of Omite. In general, the report concluded that comparison of other products from both the S-9 and homogenate metabolic conditions "did not yield any clear, quantifiable differences between the three species under study."

A copy of the proposed metabolic pathway for Propargite is attached.

Conclusion:

This study is SUPPLEMENTARY. In vitro metabolism studies provide useful information but in order to meet the requirements for a GUIDELINES metabolism study, an in vivo study must be presented.

Attachment

PROPOSED PATHWAY FOR METABOLISM OF CMEE[R] IN RATS

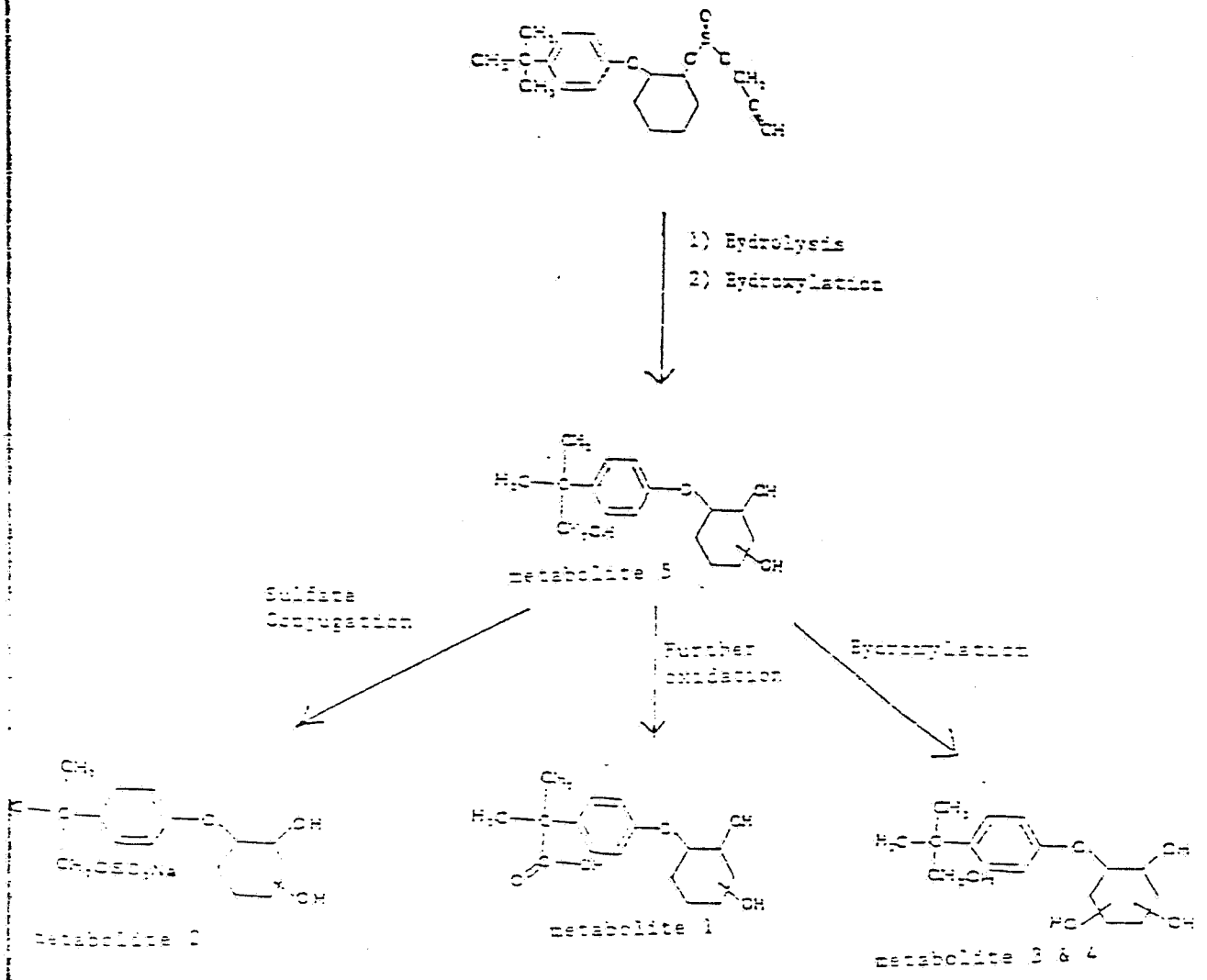

Figure 6.

Reviewed By: John Doherty 5/9/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Edwin Budd 5/16/89
Section I, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Series 85: Metabolism - Rats, Monkeys, and Rabbits

TOX Chem No.: 130I
MRID No.: 409825-06

Test Material: ^{14}C Propargite

Synonyms: Omite

Study Number: Project No. 8881

Sponsor: Uniroyal Chemical Company

Testing Facility: Battelle, Columbus, Ohio

Title of Report: Comparative Metabolism Study in Female Rats, Rabbits, and Monkeys Following a Single Oral Administration of ^{14}C-Omite.

Author: Jerry D. Johnson

Report Issued: December 29, 1988 (letter reporting results)

Conclusions:

No conclusions made (See review next page).

Classification:

CORE-INVALID (Submitted as a preliminary report).

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement: None provided.

Review

This study was submitted as a report containing information that "pertains to the on-going study." The report is in the form of a letter (dated December 29, 1988 from Jerry D. Johnson of the Battelle Laboratory to Arthur M.P. Doweyko of the Uniroyal Corporation). The letter outlines some of the procedures used as well as presents summary tables that "reflect the results of the study to date." Dr. Johnson states that until all the remaining samples are analyzed "it is difficult to provide you with any substantial evaluation of these results." Some additional information related to this study was presented in the summary of the submission prepared by Arthur M. Doweyko and N.J. Tortora (dated January 1989). This report also, however, refers to the preliminary nature of the data (refer to page 7 of the summary).

Because of the preliminary nature of the report and because of the incomplete presentation of the methodology used as well as the failure to present the report in a manner consistent with the current Guidelines for metabolism studies, TB-I considers the report INVALID. The registrant should be advised to consult with the GUIDELINES for toxicity studies for the format in presenting the data.

The registrant should also be advised that five animals of each sex for each test condition should be used for the Metabolism study. Since only one female was used per condition, it is unlikely that this study can be upgraded to CORE GUIDELINES. The data, however, may be upgraded to an acceptable level pending receipt and review of the final report and when taken together with other metabolism data with propargite.